Chapter 4

Genetic Determinants of Heart Rate Variation and Cardiovascular Diseases

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1. Introduction

Heart rate (HR) is a variable parameter that rapidly adjusts to changing hemodynamic demands (Fig. 1). HR is determined by several mechanisms. First, chronotropic regulation of the heart occurs through spontaneous and periodic depolarization of sino-atrial (SA) pacemaker cells. The activity of the SA node is modulated by the autonomic nervous system, intrinsic cardiac nervous system, baroreflexes, and respiration. Second, the sympathetic nervous system (SNS) stimulates postganglionic sympathetic nerve fibers and triggers norepinephrine release in the SA node that results in an increase in HR. Third, the parasympathetic nervous system (PNS) also plays a significant role in regulation of HR. Parasympathetic vagal nerve endings release acetylcholine, which binds to muscarinic cholinergic receptors on pacemaker cells, causing opening of potassium channels, hyperpolarization of the membrane, and, consequently, a decrease in HR. Fourth, humoral and mechanical signals have an effect on HR and its variability. Mechanoreceptors in the atrium respond to stretch (occurs during respiration) and change HR without neural input [1]. Changes in blood pressure (BP) impact HR via baroreceptor reflexes. In response to high BP, stretch-sensitive receptors in the carotid sinus and aortic arch send action potentials via the vagus and glossopharyngeal nerves to the solitary tract nucleus (NTS) of the brainstem. The NTS affects the ventrolateral medulla is causing an inhibition of sympathetic drive and activates the PNS by triggering the nucleus ambiguous. The result is a decrease in HR and BP. In response to hypotension, the baroreceptor reflex works in the opposite direction, leading to an increase in sympathetic drive and decrease in vagal tone, which raises HR and BP. Mechanical signals also lead to respiratory sinus arrhythmia – increased in HR during inhalation and decreased HR during exhalation. This normal physiologic phenomenon involves an

increase in intrathoracic volume during inspiration that results in an increase in HR by activation of SNS and a decrease in parasympathetic tone. The integrated spectral power of high frequency (HF, >0.15Hz) HR variability (HRV) is used as an index of the level of parasympathetic activity. Low frequency (LF, 0.04–0.15Hz) power of HRV reflects both sympathetic and parasympathetic activity and the LF/HF ratio is an indicator of sympatho-vagal balance [2]. Body temperature plays a relatively minor role in HRV. It has been shown that hypothermia is associated with bradycardia (decrease in HR) and fever associates with tachycardia (increase in HR) in neonates [3]. However, the contribution of baseline HR to HRV is relatively small. Very low and ultra low frequency ranges of HRV indicate alterations in body temperature.

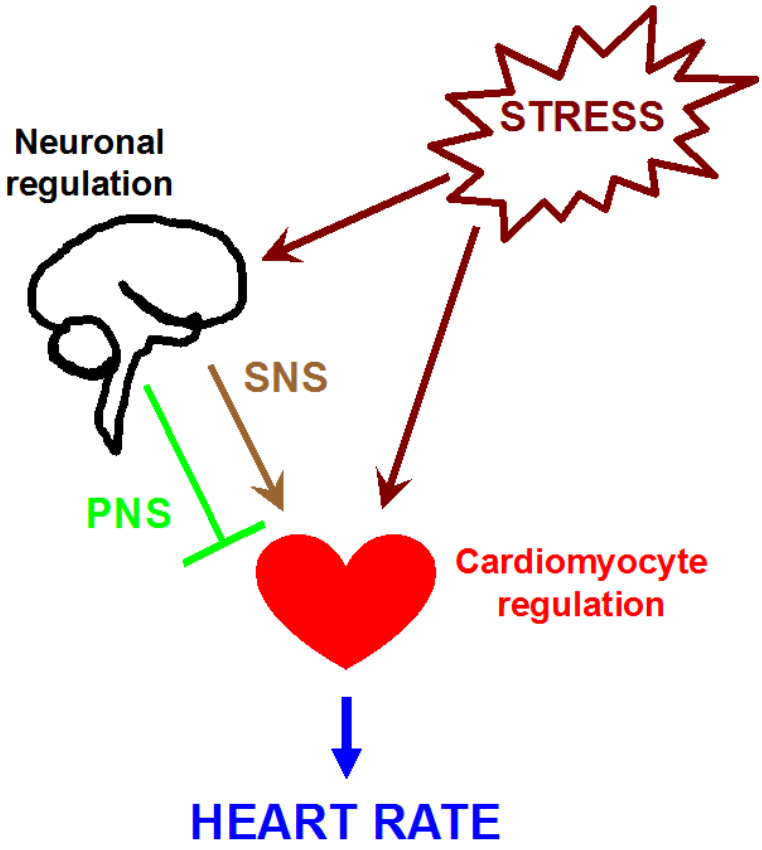

Figure 1. A scheme that shows regulation of heart rate. Heart rate (blue color) is determined by there major components. First, cardiomyocyte regulation (red color) is driven by depolarization of pacemaker cells. Second, neuronal regulation (black color) includes two components: sympathetic nervous system (SNS; brown color) and parasympathetic nervous system (PNS; green color). Third, stress factors (dark red color) are important for modulation of the heart rate. Please, see text for details.

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Increased HR has been shown as a predictor of cardiovascular mortality in healthy people, myocardial infarction (MI) and heart failure patients [4]. The increased mortality observed with an increased HR may be a consequence of the SNS/PSN imbalance that can be characterized by SNS predominance, vagal depression, or the combined impact of this dysregulation of cardiovascular function [5]. Elevated HR increases short-term cardiac output and myocardial oxygen consumption, while simultaneously reducing time of diastole and myocardial blood supply that leads to development of myocardial ischemia and arrhythmias [6]. Analysis of HRV data has provided clinically useful information about the status of the cardiovascular system. For example, *Fourier* spectral analysis of HR data has shown that frequency profiles of HRV are altered in hypovolaemia, heart failure, hypertension, coronary artery disease, angina and MI [7-12]. Acute brain injury has been linked to decreased HRV as well [13]. Chronic pathological conditions like diabetes, hyperglycemia, hyperlipidemia, obesity, and kidney failure are shown to lead to autonomic dysregulation of HR and usually associates with low HRV values [14]. Inoue and colleagues [15] showed that for every 10 beats per minute (beats/min) increase in HR, the odds ratio of an increase in white blood cells is approximately 1.3 in both men and women. These findings indicate that resting HR is clinically important for chronic inflammation and future cardiovascular events. Numerous studies have demonstrated a strong association between decreased HRV and sepsis [16, 17]. HRV is also altered in psychiatric disorders like depression [18]. In some of these conditions abnormal HRV appears to be linked to an over-activation of the SNS and hypothalamic-pituitary-adrenal axis [19].

Given the complexity of HR regulation it is difficult to understand pathological mechanisms that alter HR. As shown in other complex traits, genetic factors play an important role in HR and HRV in humans. For example, Singh et al. [20] reported that heritability might explain a substantial proportion of the variance in HR and HRV based on twin study. Here, we summarize the current facts on the genetic mechanisms of HR regulation and discuss the potential impact of HR genes on progression of cardiovascular diseases.

2. Body

2.1. Genetics of HR trait in humans

The majority of clinical studies have focused on electrophysiological abnormalities in the heart (e.g., long QT syndrome) because of their importance in sudden death [21]. However, we still have an incomplete view on the genetic contribution to resting HR variation. For the past decade genetic studies in humans revealed a number of genomic loci that control HR variation (Table 1). A first linkage analysis for resting HR was performed in 962 Caucasians and 1,124 African-Americans in the Hypertension Genetic Epidemiology Network (HyperGEN) cohort [22]. A major locus was detected on chromosome 4 (195.06cM) with logarithm of odds ratio (LOD) score of 3.18 for both racial groups. This study also indicated that chromosome 10 may harbor a locus that contributes to HR [22]. Martin et al [23] investigated a population that contained 2,209 normotensive and hypertensive individuals. The authors re-

ported ~26% heritability and found a significant locus on human chromosome 4 (128Mb; LOD=3.9). Ankyrin-B (ANK2) and myozenin 2 (MYOZ2) were proposed as candidate genes for variation in resting HR. ANK2 promotes targeting of ion channels to the membranes in cells. MYOZ2 may play a significant role in cardiac activity via excitation-contraction coupling. Thus, MYOZ2 may indirectly influence calcium signaling and pacemaker function in the heart. In a larger study of 3,282 Caucasian and African-American populations (Family Blood Pressure Program) two loci were found [24]. A significant locus on chromosome 10 (142.78cM; LOD=4.6) was linked to HR in the Caucasian group of HyperGEN. However, a common region on chromosome 5p13-14 (LOD=1.9) influenced HR in both races [24]. Genome-wide linkage for HR showed a peak on chromosome 18 (77cM; LOD = 2.03) in 73 Mongolian families [25]. Two genes SLC14A2 (solute carrier family 14 urea transporter) and LIPG (endothelial lipase precursor) are likely candidates in the chromosome 18 locus. The second peak (LOD=1.52) was identified on chromosome 5 (216cM). These findings further support the importance of the genes on human chromosome 5 for HR regulation (Table 1). The identified genomic region contains NSD1 (nuclear receptor SET domain-containing gene 1) gene that enhances transactivation of the androgen receptor. This region also contains F12 (coagulation factor XII) gene and is associated with cardiac risks [25]. The analyses of HR (measured as the RR interval) in 2,325 individuals from three isolated European populations revealed a significant locus on chromosome 12 [26]. In particular, two intronic single nucleotide polymorphisms (SNPs) (rs885389 and rs1725789) were located in a G-protein–coupled receptor 133 (GPR133) gene on chromosome 12 that exceeded the threshold of genome-wide significance ($P=3.9x10^{-8}$ and $1.5x10^{-7}$, respectively). For rs885389, each risk allele brings a decrease in 14ms in the length of the RR interval, and for rs1725789 – decrease in 16ms [26]. A significant quantitative trait locus (QTL) for HR (chromosome 9p21; LOD=4.8) was reported in the Strong Heart Family Study [27]. The linkage analyses were performed for HR, which was measured by electrocardiogram and echocardiograph Doppler recording in this population. Six significant SNPs were identified (rs7875153, rs7848524, rs4446809, rs10964759, rs1125488 and rs7853123) and the rs7875153 provided the strongest evidence for association and is located within a hypothetical protein with an undefined function (KIAA1797). However, KIAA1797 interacts with vinculin (VCL), which is involved in development of dilated cardiomypathy. Several genome-wide linkage studies assessed the involvement of the genetic factors in exercise HR response to training [28, 29]. In particular, the HERITAGE Family Study identified several genetic loci in 99 white and 127 black families [28]. Interestingly, there were differences in genetic loci between two races for baseline resting HR: for white families – chromosomes 4 and 11, for black – 2, 6, 7, 12, 14 and 15. For training HR response the following loci were identified: for white families – chromosomes 1 and 21, while loci on chromosomes 3, 20 and 21 were found in black families [28]. A follow up analysis of this cohort identified two SNPs that are located in the 5'-region of the cAMP-responsive element-binding protein 1 (CREB1) gene on chromosome 2 [29]. Most recently, the same group reported SNPs in nine genes (including CREB1) that explain heritability of training HR in the related to HERITAGE Family Study [30]. The proposed candidate genes might regulate cardiomyocyte and neuronal cell functions, as well as cardiac memory formation, fully accounting for the heritability of the submaximal HR training response.

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Chromosome	Study	Reference
2	HERITAGE Family Study	An et al, 2006 Rankinen et al, 2010 Rankinen et al, 2012
4	Hypertension Genetic Epidemiology Network (HyperGEN) Metabolic Risk Complications of Genes Obesity Project HERITAGE Family Study	Wilk et al, 2002 Martin et al, 2004 An et al, 2006
5	Family Blood Pressure Program	Laramie et al, 2006
6	HERITAGE Family Study meta-analysis of 15 GWA studies	An et al, 2006 Eijgelsheim et al, 2010
7	HERITAGE Family Study meta-analysis of 15 GWA studies	An et al, 2006 Eijgelsheim et al, 2010
9	Strong Heart Family Study in American Indians	Melton et al, 2010
10	Hypertension Genetic Epidemiology Network (HyperGEN) Family Blood Pressure Program	Wilk et al, 2002 Laramie et al, 2006
11	HERITAGE Family Study meta-analysis of 15 GWA studies	An et al, 2006 Eijgelsheim et al, 2010
12	HERITAGE Family Study 3 isolated European populations meta-analysis of 15 GWA studies	An et al, 2006 Marroni et al, 2009 Eijgelsheim et al, 2010
14	HERITAGE Family Study meta-analysis of 15 GWA studies	An et al, 2006 Eijgelsheim et al, 2010
15	HERITAGE Family Study	An et al, 2006
18	Mongolian Family Study	Gombojav et al, 2008

Table 1. Heart rate controlling genetic loci in humans

Genome-wide association (GWA) studies became a powerful approach to identify common variants associated with cardiovascular diseases. A recent meta-analysis of 15 GWA studies for HR variation included 38,991 subjects of European ancestry [31]. Authors used an adjusted RR interval for association analyses in approximately 2.5 million genomic markers. Six novel associations with resting HR were found: 6q22; 14q12; 12p12; 6q22; 7q22; and 11q12. Locus 6q22 is near a gap junction protein, alpha 1 (GJA1) gene that encodes connexin-43 protein and is crucial in electrical coupling of the myocytes. Mutations in GJA1 cause an inherited hypoplastic left heart syndrome. The second locus on 6q22 is located near SLC35F1 that encodes hospholamban. The 14q12 locus is near myosin heavy chain-6 protein (MYH6), which is related to hypertrophic cardiomyopathy, atrial-septal defects and dilated cardiomyopathy. The locus on chromosome 12p12 includes several genes (SOX5, c12orf67, BCAT1,

LRMP and CASC1) without any pathophysiological association with cardiac diseases. In the 7q22 locus a candidate gene, SLC12A9, encodes a cation-chloride co-transporter-interacting protein was found. Finally, the 11q12 locus is near FADS1 (arachidonyl-CoA) gene, which has been shown to release Ca^{2+} from the sarcoplasmic reticulum. Previously published associations were confirmed for GJA1, MYH6 and CD34. These variants explain approximately 0.7% of RR interval variance. Only 1.6% of resting HR variance can be explained by 20 polymorphisms in this study [31]. The latter suggest a substantial polygenic nature of the resting HR trait. Despite great progress in our understanding of the genetics of HR variation we have a limited knowledge of the genetic causes.

2.2. Genetic studies of HR trait in rodents

Utilization of laboratory animals has been successful in uncovering genetic causes of cardiovascular diseases. One of the major advantages of animal studies is that they have minimal environmental and methodological effects as compared to human studies. Historically, genetic crosses between two inbred lines with a robust cardiovascular variation are widely used to identify QTLs in rodents (Table 2). Studies in rats have been aimed at understanding the genetics of BP variation by using spontaneously hypertensive rats (SHR), stroke-prone spontaneously hypertensive rats (SHRSP) and Dahl rats (salt-sensitive hypertension). However, several genetic crosses uncovered QTLs that control HR trait independently from BP (Table 2). For example, HR variation after 12 days of salt-load was tested in the cross between SHRSP and Wistar-Kyoto rats (WKY), and identified a significant locus (LOD=5.9) on rat chromosome 3 [32]. In the center of the locus is SNC2α1 gene that encodes a brain isoform of α1 polypeptide of the type 2 voltage-gated sodium channel. In a cross between SHR and normotensive Brown-Norway (BN) rats a significant locus that controls elevated HR was found on rat chromosome 8 (6.8cM; LOD= 8.7) [33]. This segment of rat chromosome 8 harbors over 200 genes. The more likely candidates for HR are subtypes of nicotinic acetylcholine receptor α3 (CHRNA3), α5 (CHRNA5), and β (CHRNB4); hyperpolarization-activated channel (HCN4); 5-hydroxytryptamine (serotonin) receptor 3A (HTR3A) and 3B (HTR3B); and sodium channel (SCN2). Studies on congenic strains with varying segments of chromosome 2 between SHR and WKY rats identified a new HR locus [34]. Another congenic strain of chromosome 10 from Dahl rat revealed increased HR and short QT interval loci [35]. Authors found that overexpression of a candidate gene, rififylin (RFFL), increased cardiomyocyte beating in congenic rats. In addition to resting HR, one genetic study examined a stress-related HR variation in WKY and SHR cross progeny with 23 recombinant inbred rat strains (HXB-BXH) [36]. Specifically, genetic loci that are involved in HR responses to stress (an airpuff startle test) are located on rat chromosomes 1, 2 and 10. BN allele on rat chromosome 2 (D2Rat62-D2Rat247, LOD=2.9) enhanced the bradycardia in early response to the stress. Two significant QTLs for tachycardia responses were identified on rat chromosome 1 (D1Rat287-D1Rat292, LOD=3.1) and chromosome 10 (D10Rat26- D10Rat267, LOD=2.4). Thus, seven loci were identified in hypertensive rat models that are specific to HR variation with minimal effect from BP.

Chromosome	Study	Reference
Rat		
1	WKY x SHR cross and 23 HXB-BXH strains	Jaworski et al, 2002
2	WKY x SHR cross and 23 HXB-BXH strains Congenic SHR	Jaworski et al, 2002 Alemayehu et al, 2002
3	SHRSP x WKY cross	Kreutz et al, 1997
8	BN x SHR	Silva et al, 2007
10	WKY x SHR cross and 23 HXB-BXH strains Congenic Dahl	Jaworski et al, 2002 Gopalakrishnan et al, 2011
Mouse		
1	BALB x CBA cross C57BL/6 x DBA/2 cross	Sugiyama et al, 2002 Blizard et al, 2009
2	BALB x CBA cross	Sugiyama et al, 2002
4	FVB/NJ x 129P2 sensitized mutants cross	Scicluna et al, 2011
5	30 Inbred strains and 29 AXB-BXA strains C57BL/6 x DBA/2 cross	Howden et al, 2008 Blizard et al, 2009
6	30 Inbred strains and 29 AXB-BXA strains	Howden et al, 2008
7	C3HeB x SJL cross, 30 Inbred strains and 28 AXB-BXA strains	Smolock et al, 2012
15	BALB x CBA cross C57BL/6 x DBA/2 cross	Sugiyama et al, 2002 Blizard et al, 2009

Table 2. Heart rate controlling genetic loci in rodents

Mouse studies identified HR genetic loci that independent of BP variation (Table 2). Three significant QTLs were identified on mouse chromosomes 1, 2, and 15 in the BALB/CJxCBA/J backcross [37]. The HR quantitative trait 1 (Hrq1) locus was found on mouse chromosome 2 (72cM; LOD=4.0) and Hrq2 on chromosome 15 (25cM; LOD=3.1). The chromosome 2 locus contains a cholinergic receptor, nicotinic, polypeptide alpha 1 (CHRNA1) gene. Two of the muscarinic receptors are also the Hrq1 locus, CHRM4 (cholinergic receptor, muscarinic 4) and CHRM5. The authors also found the Hrq3 locus on chromosome 1 that significantly interacts with the Hrq1 locus [37]. Electrocardiographic evaluation of 26 AXA/BXA recombinant mouse inbred strains and linkage analyses revealed HR and HRV loci [38]. The most significant QTL for HR was found on mouse chromosome 6 (54Mb, LOD=3.8). This locus contains several candidate genes associated with HR regulation, including corticotropin-releasing factor receptor 2 (CRHR2) and neuropeptide Y (NPY). This study also uncovered a HF-HRV locus that was identified on mouse chromosome 5 (54Mb, LOD=3.1). Candidate genes for HF-HRV included D5 dopamine receptor (DRD5), peroxisome proliferative-activated receptor-coactivator-1 (PCG1),

and endothelial nitric oxide synthase (ENOS). Two significant QTLs were reported in a cross between C57BL/6J and DBA/2J strains [39]. In particular, a female-specific locus was found on mouse chromosome 1 (72cM, LOD=7.9) and gender-uniform locus on mouse chromosome 5 (54cM, LOD=8.5). A repeaded HR measurements showed a locus for HR on chromosome 15 (2cM, LOD=3.1). Importantly, two significant QTLs for HR were confirmed in BXD recombinant inbred strains. L-type calcium channel (CAV1.1) and regulator of G protein signaling (RGS2) are the two candidate genes within the HR locus [39]. A linkage analysis for HR variation in a sensitized mouse mutant ($SCN5A\text{-}1798^{insD/+}$) was studied in F2 progeny from the FVB/NJx129P2 cross [40]. Interval mapping found a HR locus on chromosome 4 (136-151Mb, LOD=4.2). Finally, we reported a highly significant QTL for elevated HR on chromosome 7 (41 cM, LOD = 6.7) in the C3HeB/FeJxSJL/J backcross [41]. We mapped this locus using a GWA analyses in the Hybrid Mouse Diversity Panel (HMDP) that included 30 inbred and 28 AXB/BXA recombinant inbred strains. We detected seventeen significant SNPs within a 0.9Mb interval on mouse chromosome 7. This locus contains a cluster of three gamma-Aminobutyric acid (GABA) A receptor subunit genes: GABRβ3, GABRα5, and GABRγ3. These receptor subunits are responsible for inhibitory effects of neurotransmitter $GABA_A$ in the brain. Taken together, animal studies yielded a similar number of the genetic loci as reported in humans for HR variation.

2.3. Challenges and future directions in the genetic studies on HR variation

Despite the progress in technology of the high throughput wide-genome screens in human populations, the methodological challenges are attributed to variability of HR. In addition, BP levels and/or responses to therapy may further limit our abilities to dissect the genetic basis of HR variation in humans. For example, retrospective analyses of several anti-hypertensive trials revealed potential methodological differences [42]. Specifically, clinical, ambulatory and home monitoring methods might introduce inter-individual variability that could complicate genetic analyses. One approach is to increase the number of the assessments of hemodynamics per individual. For example, repeated measurements have improved reproducibility between the measurements taken on the same day and between days in heart failure patients [43]. Therefore, more uniform methods of evaluation of HR trait should be considered in large genetic studies in humans. Animal experiments are proven as better-controlled genetic models for complex traits. However, there are similar genetic loci identified on the HR trait between human and animal studies (Tables 1-2). The latter suggests a clear need for more genetic experiments in animal models. GWA and traditional genetic approaches (genetic intercrossed and congenic lines) should improve mapping results. We recently combined two approaches and mapped a novel genetic locus on mouse chromosome 7 that contains three candidate genes [41]. Overview of the current candidate genes suggests involvement of three major components in HR regulation: 1) cardiomyocyte cell function; 2) neuronal cell functions; and, 3) stress-related pathways (Fig. 1). So far only a limited number of HR candidates were validated in genetically targeted animal models. In particular, mice heterozygous for ANK2 that phenocopy human sinus node dysfunction, displayed severe bradycardia and HRV [44]. Several mouse mutants were made to target a class of hyperpo-

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larization-activated cyclic nucleotidegated (HCN) cation channels [45]. It was concluded that the HCN4, HCN1 and HCN2 subunits are important for generation of the pacemaker current in the SA cells [45]. RGS2 knockout mice exhibited autonomic abnormalities in regulation of hemodynamic parameters [46]. Authors found that RGS2 knockout mice had an increased sympathetic tone and exhibited baroreceptor-HR reflex resetting. In addition, two HR candidates were implicated in stress-dependent responses [47, 48]. First, studies in CRHR2 knockout mice suggest its involvement in stress-responses in the brain and periphery [47]. Second, mice that overexpressed NPY showed enhanced sympatho-adrenal activity and adaptive responses to various stresses [48]. Although gene targeting is widely used in mice, transgenic rats can be generated by zinc-finger nucleases [49]. A recent report showed successful generation of a renin knockout rat on the Dahl salt-sensitive background [50]. However, development of systems genetics approaches would dramatically elevate our understanding of the contribution of the each regulatory component of HR variation. We think that utilization of systems biology approaches will provide significantly more insights into HR variation [51]. Ultimately, validation of the HR candidate genes and pathways in animals will validate HR studies in humans. These research efforts may lead to personalized diagnostic and treatment strategies for cardiovascular patients.

3. Conclusions

HR is regulated by very complex mechanisms (Fig. 1). Abnormal HR is a strong predictor for cardiovascular diseases. However, pathophysiology of HR regulation is not well understood. It is also well established that genetic factors play an important role in HR variation. Genetic studies in humans identified over 20 loci that are linked to the HR trait. Despite the recent progress we can explain only a small portion of the genetic contribution to HR variation. Inter-individual variability in hemodynamic parameters remains one of the key challenges in large population studies. In fact, identification of the stress-related genes may suggest that the methods of evaluation of HR might affect the stress-response in humans. Genetic experiments in animals significantly reduce effects of the environmental/methodological factors. However, only a similar number of the HR loci were identified in rodents compared to humans (Tables 1-2). Overview of the candidates revealed that they contribute to the HR variation via three major mechanisms: cardiomyocyte, neuronal cell functions and stress-responses. In general, there is a lack of validation of both, human and animal studies. We think that generation of transgenic animal models of HR candidate genes should also be coupled with systems genetics approaches. Experimental studies will lead to translational applications for preventing cardiovascular diseases related to HR pathophysiology.

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Abbreviations

HR, heart rate

SA, sino-atrial (cells/node)

SNS, sympathetic nervous system

PNS, parasympathetic nervous system

BP, blood pressure

NTS, solitary tract nucleus

HF, high frequency

HRV, heart rate variation

LF, low frequency

MI, myocardial infarction

LOD, logarithm of odds ratio

SNP, single nucleotide polymorphism

QTL, quantitative trait locus

GWA, Genome-wide association

SHR, spontaneously hypertensive rats

SHRSP, stroke-prone spontaneously hypertensive rats

Dahl, salt-sensitive rats

WKY, Wistar-Kyoto rats

BN, Brown-Norway rats

HMDP, hybrid mouse diversity panel

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